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# Implementation of the Harmonized EU Isotretinoin Pregnancy Prevention Programme

## A Questionnaire Survey among European Regulatory Agencies

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### Abstract

**Background:** There is little information on the status of the implementation of the isotretinoin Pregnancy Prevention Programme (PPP) in the EU, and on compliance with this programme by the regulatory agencies.

**Objective:** The aim of the study was to obtain information on implementation of the harmonized PPP of isotretinoin in the EU member states plus Norway and Iceland.

**Materials and Methods:** In January 2009, a questionnaire (request for non-urgent information [NUI]) was sent to all 25 EU member states, plus Norway and Iceland, to collect information on the implementation status of the PPP and its effectiveness.

**Results:** The response rate was 82% (22 of the 27 countries). In 21 of the 27 member states, isotretinoin is marketed and the PPP is in force, and in 18 of the 22 responding countries, the total required elements (seven) following a formal EU review are incorporated in the PPP. Seven member states had additional measures in place. In spite of implementation of the PPP and additional measures, a total of 143 isotretinoin-exposed pregnancies have been reported in 16 of the 22 responding member states since implementation of the harmonized PPP.

**Conclusions:** Despite implementation of the isotretinoin PPP in most member states, isotretinoin-exposed pregnancies were reported. This has led some member states to implement additional measures to the PPP, resulting in inconsistency with the approach agreed in 2003 following the European-wide review. It has been further suggested that common elements should be developed for PPPs for all medicines that are known to carry a high teratogenic risk.

## Background

Isotretinoin is a vitamin A derivative, licensed in the EU for the treatment of severe acne that has not responded to other treatments.<sup>[1]</sup> Like all vitamin A derivatives, isotretinoin is highly teratogenic; the rate of teratogenicity of vitamin A derivatives is comparable to the rate of teratogenicity of thalidomide.<sup>[2]</sup>

In 1982, isotretinoin was licensed in the US and labelled a category X medication (agents that have demonstrated clear risk of fetal abnormalities and whose risks outweigh the benefits of use during pregnancy<sup>[3]</sup>). The isotretinoin embryopathy consists of craniofacial, cardiac, thymic, and CNS defects, and occurs in an estimated 26% of exposed patients.<sup>[2]</sup> Exposure of isotretinoin beyond the critical period,<sup>[2]</sup> i.e. the first 10 weeks following conception, which is associated with the above-mentioned embryopathy, can cause developmental delays and other CNS effects at even higher frequencies of approximately 40%.<sup>[4,5]</sup>

Despite warnings to avoid use of isotretinoin in pregnancy, the first cases of congenital anomalies associated with isotretinoin use were published in 1983.<sup>[6]</sup> Isotretinoin has been licensed for use in the EU since 1984, and a Pregnancy Prevention Programme (PPP) for isotretinoin was implemented by the Marketing Authorization Holder (MAH; Roche) in 1988<sup>[7]</sup> to minimize the risk of embryopathy. The isotretinoin PPP consisted of five elements:

- a guidance document for physicians;
- checklist for prescribing to female patients;
- patient information brochure;
- contraception brochure;
- patient informed consent form.

In 2003, generic formulations of isotretinoin entered the market. Following a European-wide review and a European Commission (EC) decision, an EU PPP was agreed that is applicable to all MAHs for isotretinoin products.

Following the EC decision in 2003,<sup>[1]</sup> the PPP was revised to contain the previous five elements, as well as a guidance document for pharmacists and more specific educational material for patients. The indication for use of isotretinoin was also restricted to its second-line use in the treatment of “severe forms of acne resistant to ade-

quate courses of standard therapy with systemic antibacterial medication and topical therapy”, in contrast to its previous indication for the first-line treatment of “severe cystic acne and acne conglobata and acne resistant to other therapies”.<sup>[8]</sup>

Despite implementation of the EU PPP, pregnancies have still been reported during isotretinoin use,<sup>[9,10]</sup> and this has led to several initiatives to enhance the efficacy of the PPP in EU countries. Information on the status of implementation of the harmonized PPP in EU member states, plus Norway and Iceland, as well as other information available might provide a basis for improved risk minimization.

The aim of this study was therefore to evaluate the status of current European-wide implementation of, and compliance with, the isotretinoin PPP by the EU member states, plus Norway and Iceland, by circulating a questionnaire, or non-urgent information (NUI) request,<sup>[11]</sup> to the EU member states plus Norway and Iceland.

## Materials and Methods

On 26 January 2009, an NUI request was circulated to the competent authorities of the 25 EU member states plus Norway and Iceland, to collect available information on the implementation of, and compliance with, the isotretinoin PPP by the EU member states plus Norway and Iceland. Three weeks after sending the NUI, a reminder was circulated. Last responses were received 7 weeks after the first mailing.

Circulating an NUI to the EU member states is an established method for exchange of information between national competent authorities in the member states and the European Medicines Agency on safety issues. The purpose of an NUI is either to inform, or to obtain information, for instance via questionnaire, from the other member states on the status of a specific safety issue. In the latter, a report compiled from the responses can then be used for a discussion in the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use of the EC on this specific safety issue.

This current NUI consisted of seven questions (see table I). The responses were collected and

**Table I.** Questionnaire for evaluating implementation of the EU isotretinoin Pregnancy Prevention Programme (PPP)<sup>[1]</sup> in the EU member states circulated as a non-urgent information<sup>[11]</sup> request to member states

1. Are isotretinoin medicinal products authorised and marketed in your country? If yes, please specify.
  2. Have you implemented a Pregnancy Prevention Programme (PPP)<sup>a</sup> for isotretinoin? If yes, for which products?
  3. Does the PPP(s) for isotretinoin contain the following materials:
    - I. Pharmacist's Guide to dispensing isotretinoin
    - II. Physician's Guide to prescribing isotretinoin
    - III. Checklist for prescribing to female patients
    - IV. Educational material for the male and/or female patients
    - V. Patient information brochure
    - VI. Brochure on contraception
    - VII. An acknowledgement form for female patients
  4. Was there additional material? If yes, please specify.
  5. Are you aware of any isotretinoin-exposed pregnancies in your country? If yes, were any pre-emptive measures taken to prevent more isotretinoin-exposed pregnancies.
  6. Do you consider the national PPP satisfactory? If no, please specify
  7. Do you have other relevant information?
- a Because of a European Commission decision in October 2003,<sup>[1]</sup> the European member states should implement a defined PPP for isotretinoin-containing products in their country.

discussed during a meeting of the PhVWP on 16 March 2009.

Descriptive statistics were used to analyze the responses.

## Results

Twenty-two of the 27 countries (82%) participating in the European regulatory network responded to the NUI request on implementation of the isotretinoin PPP.

Isotretinoin is marketed in 21 of the 22 responding member states (Sweden was the only exception). The original product of Roche (Roaccutane<sup>®</sup>) was licensed in 16 countries, of which 13 countries also subsequently licensed one or more generic formulations of isotretinoin. In Sweden, the product is not licensed for use, but can be prescribed on a named-patient basis. In five countries, only generic formulations of isotretinoin are licensed, and the majority of the licensed isotretinoin products were also marketed. The median number of different isotretinoin products marketed per EU

member state (different dosages are pooled) is 4 (range 0–12).

The current EU PPP has seven elements, and in 18 countries all seven elements are implemented. Three countries did not effectuate the educational material for patients and, in addition, one of these three countries did not have the contraception brochure.

Seven countries had additional material as well as the agreed European PPP materials. The additional material consisted of a patient booklet that patients presented at each prescriber and pharmacist visit in order to follow-up and ensure that all requested information (pregnancy test: date and result, contraceptive status) was provided before prescription, during prescription and during dispensing, and a questionnaire or a pregnancy follow-up form. One of the other countries with additional material had implemented an additional measure that all women of child-bearing age should have consulted a gynecologist before starting treatment with oral isotretinoin.

Responses to the question on awareness of isotretinoin-exposed pregnancies and eventual pre-emptive measures were not answered consistently and the results are therefore difficult to analyze. One country reported an increase in pregnancies in percentages (which have been published elsewhere<sup>[9]</sup>), instead of the absolute number of pregnancies. The number of pregnancies was reported over different time periods: either since launch, or after implementation of the agreed EU PPP. Since the marketing of isotretinoin in all responding countries, the reported number of pregnancies related to isotretinoin exposure was 393 in total (range per country 0–289). Following implementation of the EU PPP (from 2003 to the beginning of 2004), 143 pregnancies (range per country 0–65) related to isotretinoin exposure were reported. Five countries reported zero pregnancies and one country did not have data available. The 289 pregnancies reported in one country included 65 pregnancies following implementation of the current PPP. Agencies have published information on reported cases of isotretinoin-exposed pregnancies in their national medical journal or on their website, or instigated review by their National Drug Safety Committee.

Overall, eight countries reported that they were satisfied with the isotretinoin PPP, while nine countries were not. Two countries expressed doubt on the effectiveness of the PPP, another two countries stated that research is ongoing and that at that moment no opinion could be expressed, and one country abstained from answering this question.

The last question, whether there was other information relevant to the implementation of, and compliance with, the isotretinoin PPP elicited information on additional activities undertaken by each country. In two countries, Dear Healthcare Professional Communication (DHPC) letters were sent reminding physicians about the PPP and reminding pharmacists on dispensing restrictions. In one country, a policy had been implemented, restricting the prescription of isotretinoin to dermatologists only. One country was assessing the content of educational materials. In another country, a cross-sectional study was conducted in January 2008 to assess compliance with PPP recommendations. The results of this study<sup>[12]</sup> showed that healthcare professionals were aware of the teratogenicity of isotretinoin, but were not compliant with the recommendations of the PPP, and that women of childbearing potential were not informed of the risk of teratogenicity associated with the use of isotretinoin during pregnancy before initiating treatment.

It was also suggested by one of the member states that harmonization of PPPs for different teratogenic active substances (isotretinoin, thalidomide and lenalidomide) should be undertaken.

## Discussion

All responding member states in which isotretinoin is marketed have implemented a PPP. The fact that five countries did not respond limits the results of this investigation. Of the responding member states with a national PPP in force, 18 of 22 countries (82%) reported that the PPP contained all seven elements agreed following the European-wide review in 2003. Despite these measures, isotretinoin-exposed pregnancies continue to occur in the responding countries; however, details on these pregnancies are lacking.

Competent authorities hold different opinions as to the effectiveness of the isotretinoin PPP, and these opinions were not related in any way to the actual number of pregnancies in that country. Several member states are considering, or have already implemented, additional measures to the EU-agreed PPP on a national level.

A limitation of this investigation could be measurement at only one point in time, i.e. at the beginning of 2009. However, from information provided by MAHs in their periodic safety update reports, it is known that implementation status is still valid. Moreover, it is possible that socially favourable answers were given by some countries to present their results in a more positive light.

As a post-authorization commitment following the regulatory referral in 2003, the MAH of the original product, Roaccutane<sup>®</sup> (Roche), provided 6-monthly reports on the implementation and effectiveness of 'infoRM', the risk minimization measures in place until 2010. Currently, yearly reports are to be provided. These reports provide cumulative data of pregnancies reported to the MAH. Based on the well known limitations of spontaneous reporting, there is probably a degree of underreporting.<sup>[13]</sup> To have a complete overview, female users of childbearing age would need to be included in a register for complete follow-up. In Sweden, where isotretinoin is provided on a named-patient basis, patients can be closely monitored, and a total of 11 pregnancies have been reported during, or just after stopping, the use of isotretinoin.

The additional measures taken by some member states add to the complexity of evaluation of compliance with the PPP. Adding to the challenges faced is the fact that there are cases reported in which pregnancy occurred after careful compliance with the isotretinoin PPP.<sup>[14]</sup> An assessment of the results of the US PPP concluded that patient failure to use two contraceptive methods was the most common reason for fetal exposure.<sup>[15]</sup> Furthermore, a study in France<sup>[9]</sup> showed that in 32% of isotretinoin-exposed pregnancies no contraceptive methods had been used. From personal communication with prescribers in the Netherlands, it is known that some patients

are opposed to contraception, e.g. for religious reasons. However, withholding isotretinoin is regarded as undertreatment of these patients, leaving ethical challenges.

Half of the responding member states considered the effectiveness of the PPP to be insufficient. This leads to the question of whether the ultimate goal of a PPP should be zero exposed pregnancies, zero infants with congenital malformations or zero women who are uninformed of the risks of pregnancy during isotretinoin treatment. The incidence of congenital malformations in the general population, i.e. 2–5% of all pregnancies,<sup>[16,17]</sup> should also be taken into account.

Furthermore, the influence of public and political opinion on healthcare challenges such as this is substantial. The initiative in the US to introduce the stricter PPP, iPledge, in 2006 seems to have perpetuated the concept of zero risk of becoming pregnant during isotretinoin treatment, by implying that all congenital malformations in the isotretinoin user group are attributable to isotretinoin exposure.

The greatest challenge in all PPPs is human error, or varying levels of commitment to the use of adequate contraceptive measures. The Pearl index (measure of contraceptive failure) of various forms of contraception ranges from 0.1 to 2.5 per 100 women at 1 year.<sup>[18]</sup> In the US in 2001, 5% of women aged 15–44 years had an unintended pregnancy.<sup>[19]</sup> Pregnancy rates during isotretinoin use are lower (0.3%).<sup>[20]</sup>

To strengthen the European isotretinoin PPP, a very strict programme such as iPledge, for instance, could be initiated. Other measures might increase the effectiveness of the isotretinoin PPP, such as the use of hormonal implants for contraception, or restricting prescription of isotretinoin to dermatologists in specialized centres only. In these centres, specially trained nurses could supervise the provision of information to patients, as well as checking pregnancy test results and other tasks. Besides increasing compliance, monitoring of the effectiveness of the PPP could be more rigorously performed. In addition, greater uniformity of implementation of the PPP and of data collection within the EU member states would provide more robust results for evaluation of the

effectiveness of risk minimization measures. A harmonized, amended EU PPP should also be based on realistic goals balancing maximum compliance with a streamlined, realistic administrative workload for all involved parties.

## Conclusions

Despite challenges in assessing the effectiveness of the implementation of isotretinoin PPPs in European member states, data gathered from national competent authorities via a questionnaire survey showed a low rate of occurrence of exposed pregnancies but a significant level of concern about the effectiveness of implementation of the PPP. An amended harmonized isotretinoin PPP should be considered that has a clearly stated goal and maximum demonstrated effectiveness with rigorous uniform monitoring. It has been further suggested that common elements should be developed for PPPs for all medicines that are known to carry a high teratogenic risk.

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